Reviewer’s report

Title: Safe and effective use of nivolumab for treating lung adenocarcinoma associated with sporadic lymphangioleiomyomatosis: a rare case report

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Reviewer: Maria Jové

Reviewer's report:

The author reported a case of NSCLC in a patient previously diagnosed of lymphangioleiomyomatosis (LAM). The case report is relevant due to the lack of literature of immune checkpoint inhibitor in patients with interstitial and whether it is safety in this subgroup of patients.

However, there are a few things I would like to consider:

1. I would strongly recommend the text to be properly reviewed by an English speaking person.

2. Bibliography should follow the Vancouver style. E.g. when more than 6 authors should be state as 3 authors by et al. and some reference are incomplete.

3. In my opinion, the conclusion should focus more on the safety profile of nivolumab in this patient with previous history of LAM and which other evidence is published regarding checkpoint inhibitors and patients with interstitial lung disease. The authors suggest quite strongly that checkpoint inhibitors might have a role in LAM treatment. As far as I am concerned, there is no clinical based evidence that supports this. It should be clear which type of evidence it has.

I would further write below some specific comments that need to be clarified:

Page 5 Line 99: Add the dose and schedule for sirolimus treatment. Is the dose equivalent to the ones we used with other mTOR inhibitors for renal cancer?

Page 5 Line 100: Figure 1A instead of 1
Page 5 Line 110: You reported a mutation on BRAF. Did you perform EGFR or ALK testing? PDL1? If not, why you have tested BRAF instead?

Page 5 Line 113: Did you perform a re-biopsy at relapse?

Page 5 Line 113: Again, did you test PDL1 before or after the start of nivolumab treatment?

Page 6 Line 124: Figure 2 should be 1B

Page 6 Line 124: "Given that the pneumothorax occurred speedily after nivolumab infusion, nivolumab was not deemed responsible and this drug was thus resumed it in January 2016".

Comment: This is a quite strong statement. I do not the early onset of pneumothorax after nivolumab is a justification to not relate this complication as toxicity of nivolumab. I agree it is more likely to be due to the LAM. It is described that patients with LAM have higher incidence of pneumothorac and indeed the patient has a previous history of pneumothorac

Page 6 line 126: while gradually resuming work - I think the expression is "gradually returning to work" (Check with English speaking person, please).

Page 6 Line 128: "Treatment safety has so far been good, except for grade II hypothyroidism."

English correction: Treatment was well tolerated with no major safety issues. Patient developed grade II hypothyroidism (I guess treated with hormone replacement). Again, check the text with English speaking person.

Hypothyroidism has been reported to be a biomarker for efficacy. You might want to address or comment this in your discussion.

Page 6 Line 128: "Lung function tests and symptoms worsened".

Clarify: When? Was it slowly progressive? Which clinical symptoms? Please describe a bit more and give data and parameters that are objective.
Based on CT follow-up, this worsening was neither related to infection nor visible nivolumab-associated pneumonitis.

Clarify: Could it be a worsening of the interstitial disease (LAM) due to the nivolumab? Was any fibrobronchoscopy done? Could you provide images of the worsening ILD? Would be useful to have a picture that shows lung parenchima with LAM lesions evolution before, during nivolumab treatment and after sirolimus was reintroduced. It is relevant to see the different evolution of the cancer (Fig 1) and LAM (potentially new fig 2).

Page 6 Line 135: "LAM is a rare cause of diffuse parenchymal lung disease according to the interstitial lung disease classification [11], which has been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC"

Clarify: Confusing sentence- It is redundant. LAM is a rare cause of diffuse parenchymal lung disease [11]. Interstitial lung diseases have been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC.

Page 6 Line 139: "This common pathogenesis also constituted the rationale for using immune checkpoint inhibition in this indication, despite the lack of published data on this indication in the literature".

Comment: Too strong! Is there any preclinical data that supports this statement at least?

Page 6 line 143: "According to Klarquist [13] and Carbone [14], LAM cells bear antigenic similarities with melanoma cells, such as sharing several common immune markers. To illustrate, some LAM cells can express gp100 and other melanoma antigens (MART-1) that tend to be recognized by T-cells. Thus, the authors hypothesized that immunotherapy successfully developed against melanoma could constitute a reasonable treatment approach for LAM, despite interstitial lung disease commonly being the disease presentation mode."

Comment: Check with English speaking person, please. I guess authors thought that "theoretically" LAM could response to nivolumab but I do not think there is enough evidence for this statement. Authors should soften this association. Indeed, the patient did not respond to it. Last sentence is written a bit confusing.

Page 6 Line 134: "LAM is a rare cause of diffuse parenchymal lung disease according to the interstitial lung disease classification [11], which has been a key exclusion criterion in original immune checkpoint inhibitor studies in NSCLC"
Again check text with English speaking person.

Page 6 Line 138: This common pathogenesis also constituted the rationale for using immune checkpoint inhibition in this indication, despite the lack of published data on this indication in the literature. We weighed up the risks and benefits before using immunotherapy, and then proposed this treatment strategy to the patient; in the end, our decision proved to be congruent with the recent expert review by Postow et al. [12].

Comment: It feels like the authors considered nivolumab a possible treatment option for LAM. Again I do not think there is enough evidence. When referring to Postow et al. paper it looks like you are justifying the use of nivolumab for LAM efficacy instead of justifying safety issues.

Page 7 Line 161 "To date, the tumor response is still responding"

Redundant… Please, correct the text with English speaking person.

Page 7 Line 167 "Although sporadic LAM is a rare condition, it can be associated with NSCLC"

Comment: Quite strong association! Are any association between LAM and NSCLC? Have patients with LAM a higher risk of developing NSCLC?

Figure 1: Use the common names of the drugs and not the commercial ones to be consistent with the text.

Finally, the most striking point for me is the safety of nivolumab in a patient with LAM and concomitant immunosuppressive agent and the fact that concomitant sirolimus does not seem to have deemed the efficacy of nivolumab in this patient. There is still controversy of immunosuppressive agents concomitant with immunotherapy. Authors might want to address it.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Needs some language corrections before being published

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